Section: Pathology

Research

EVALUATION OF PROGNOSTIC INDICATORS IN COLORECTAL CARCINOMA – A COMPREHENSIVE STUDY TO CORRELATE STAGING, GRADING AND PROLIFERATIVE INDICATORS

Chinthu P[1], S. Vishnu Priya[2], Selin Sofiah C[3], Johnsy Merla J[4], J. Suresh Durai[5]

[1]Assistant Professor, Department of Pathology, Virudhunagar Medical College, Tamilnadu, India.
[2]Assistant Professor, Department of Pathology, Sivagangai Medical College, Tamilnadu, India
[3]Assistant Professor, Department of pathology, Tirunelveli Medical College, Tamilnadu, India
[4]Associate Professor, Department of Pathology, Tirunelveli Medical College, Tamilnadu, India
[5]Professor, Department of Pathology, Kanyakumari Medical College, Tamilnadu, India

Received : 10/12/2022
Received in revised form : 07/01/2023
Accepted : 17/01/2023

Keywords:
Colorectal Carcinoma, Prognosis, Ki67 proliferation index.

Corresponding Author:
Dr. Johnsy Merla J,
Email: drjohnsymerla@gmail.com
ORCID: 0000-0002-7846-920X

DOI: 10.47009/jamp.2023.5.1.119

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (1); 576-581

Abstract

Background: Colorectal cancer, also known as CRC, is a type of cancer that affects the colon and rectum. It is the third most common type of cancer worldwide. The study aims to stage different grades of colorectal carcinomas and evaluate the role of proliferative immunomarkers in each stage. **Materials and Methods:** A retrospective and prospective study were conducted at the Department of Pathology, Tirunelveli Medical College, from 2015 to 2018. A total of 42 cases of colorectal carcinoma were selected for the study, and informed consent was obtained. In addition, those specimens received in the histopathological laboratory reported as colorectal carcinoma were included. **Result:** Among 42 patients, 20 were males, and 22 were females. Thirty-four cases were found to be Adenocarcinoma, NOS type (81%), 7 cases were Mucinous adenocarcinoma (16.7%), and 1 case was Squamous cell carcinoma (2.4%). The Ki67 index calculated for the 42 cases of colorectal carcinomas ranged from 14.5% to 74.6%. The mean Ki67 index for the 14 cases of well-differentiated adenocarcinomas was 54.15%, 16 cases of moderately differentiated carcinomas were 50.83%, and 7 cases of mucinous adenocarcinomas were 33.34%. However, not all cases in the study showed a direct correlation between tumour grade, stage and Ki67 index. Eight cases (19%) had a Ki67 proliferation index that didn't correlate with their stage and grade at presentation. **Conclusion:** An immunohistochemical study of the Ki67 proliferation index in cases of colorectal carcinoma was found to provide an additional clue regarding the biological behaviour of many tumours. Furthermore, it could help predict the prognosis of colorectal carcinomas.

INTRODUCTION

Colorectal cancer, also known as CRC, is a type of cancer that affects the colon and rectum. It is the third most common type of cancer worldwide and has a high mortality rate when it reaches advanced stages.[1] Several risk factors contribute to the development of colorectal cancer, including age, gender, family history, and lifestyle choices. Advanced age is a major risk factor for colorectal cancer, as it is more common in people over 50. Men are also more likely to develop colorectal cancer than women. A family history of colorectal cancer can also increase a person's risk of developing the disease. Dietary factors also play a role in the development of colorectal cancer. A diet high in red meat, fat, and processed foods and low in fruits and vegetables is associated with increased disease risk. In addition, lifestyle factors such as obesity, smoking, and heavy alcohol consumption can increase the risk of colorectal cancer. With the increasing westernization of countries such as India, the incidence of colorectal cancer has been on the rise in previously low-incidence areas. This is likely due to changes in diet and lifestyle that have occurred as a result of modernization. Overall, it is important for individuals to be aware of the risk factors for colorectal cancer and to take steps to reduce their risk, such as eating a healthy diet, maintaining a healthy weight, and avoiding smoking and excessive alcohol consumption.[2,3]

Colorectal carcinoma is a heterogeneous disease. Three major molecular pathways have been identified leading to colorectal carcinogenesis. They are the Chromosomal instability (CIN) pathway, accounting for up to 85% of CRC (ii) Microsatellite

instability (MSI) pathway, (iii) CpG island methylator phenotype (CIMP) pathway.[4] Patients with familial colorectal carcinomas require both diagnostic testing and molecular screening. Almost 85% of colorectal cancers occur sporadically, and about 15-20% are inherited.[5] Colorectal cancers usually occur from pre-existing adenomas; hence the disease can be prevented and curable if the diagnosis is made early. Hence screening with colonoscopy, flexible sigmoidoscopy and occult blood test is essential. Colonoscopic biopsy and pathological examination remain the gold standard in diagnosing colorectal carcinoma. Imaging aids in the proper staging before surgery.

The prognosis in each case is obtained through the histopathological confirmation of the adequacy of excision, tumour stage, type and grade. Currently, Tumour, Node and Metastasis (TNM) staging system provides almost accurate prognostic information in colorectal carcinoma. The prognosis also varies with tumour type and grade. However, there is a heterogeneity in the clinical features and survival rates among the patients with the same stage. Hence the application of immunohistochemical studies with proliferation markers, such as Ki67, provides a step ahead in establishing the prognosis.

AIM

The study aims to stage different grades of colorectal carcinomas and evaluate the role of proliferative immunomarkers in each stage. The study also predicts tumour aggressiveness and biological behaviour and prognoses the disease outcome using specific cell proliferation indicators.

MATERIALS AND METHODS

A retrospective and prospective study were conducted at the Department of Pathology, Tirunelveli Medical College, from 2015 to 2018. A total of 42 cases of colorectal carcinoma were selected for the study, and informed consent was obtained. In addition, those specimens received in the histopathological laboratory reported as colorectal carcinoma were included.

Cases excluded were samples received from patients of Colorectal carcinoma who were subjected to prior chemotherapy or radiotherapy and small biopsies of cases of colorectal carcinoma. In addition, Paraffin blocks containing tissue of surgically resected colorectal carcinoma patients were collected from the archives of the Department of Pathology.

Sections stained with haematoxylin and eosin were used for histological typing and grading colorectal carcinomas. The studied 42 cases of colorectal carcinoma were classified according to WHO histological classification.[6] As Adenocarcinoma, OS type (34 cases), mucinous adenocarcinomas (7 cases) and squamous cell carcinoma (1 case). Adenocarcinomas are graded according to the degree of tubule formation and cellular array in tumour tissue as Grade 1 or Well differentiated - >95% with gland formations, tumour cells had a uniform appearance, and there is no or minimal loss of polarity; Grade 2 or Moderately differentiated - 50-95% with gland formation, tubular structures can be simple or complex as may be slightly irregular shaped, loss of nuclear polarity was evident; Grade 3 or Poorly differentiated - 0-49% with gland formation.[7] The pathological tumour staging was performed according to the American Joint Committee on cancer by grouping the various TNM components.[8] The tumour stage (T) was determined from sections that reached the pericolic fat; the nodal status (N) was also recorded from corresponding sections, and any metastasis (M) was reported from the patient file and accompanying specimens.

Tumour cell proliferation was studied by doing immunohistochemistry with Ki67 antibody. Immunohistochemical staining was done in the normal intestinal mucosa of patients in the 2nd to 7th decade who were subjected to histopathological examination and served as the control group and 42 cases of colorectal carcinoma, which was the study group. An analysis was done by correlating the Ki67 index with the stage and grade of the tumour in these 42 cases of colorectal carcinoma.

RESULTS

Among these patients, 20 were males, and 22 were females. The minimum age of presentation was 17 years, and the maximum was 76 years. The mean age of presentation was 53.95 years.

In the 42 cases, 8 cases were found in the Ascending colon (19%), 6 cases in the Caecum (14.3%), 3 cases in the Descending colon (7.1%),4 cases in the Transverse colon (9.5%), 3 cases in the Recto-sigmoid junction (7.1%), 10 cases in the rectum (23.8%), and 8 cases in the Sigmoid colon (19%). In addition, 34 cases were found to be Adenocarcinoma, NOS type (81%), 7 cases were Mucinous adenocarcinoma (16.7%), and 1 case was Squamous cell carcinoma (2.4%). In addition, 14 cases were well- differentiated (41.2%), 16 cases were moderately differentiated (47%), and 4 cases were poorly differentiated (11.8%). Three cases were in stage I (7.1%), 11 cases in stage IIA (26.2%), 6 cases in stage II B (14.3%), 5 cases in stage II C (11.9%), 1 case in stage III A (2.4%), 10 cases in stage III B (23.8%), 5 cases in stage III C (11.9%), 1 case in stage IV C (2.4%). [Table 1]

The Ki-67 index in the normal intestinal mucosa was between 2.6% and 18.2%, with an average of 9.992%. Positive nuclear immunohistochemical staining for the Ki-67 antibody was seen in all 42 cases of colorectal carcinomas. Therefore, the ki67 index was calculated for all 42 cases. The minimum Ki67 index observed was 14.5%, and the maximum index obtained was 74.6%. [Table 2]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

The mean Ki67 index for the 14 cases of well-differentiated adenocarcinomas was 54.157. Sixteen cases of moderately differentiated carcinomas were 50.838, 4 cases of poorly differentiated carcinomas were 63.950, 7 cases of mucinous adenocarcinomas were 33.343, and 1 squamous cell carcinoma was 60.10. Mucinous adenocarcinomas showed a low proliferating index. The mean Ki67 index for the 3 cases of stage I was 61.80, 11 cases of stage II A was 47.10, 6 cases in stage II B was 47.76, 5 cases in stage II C was 49.32, 1 case in stage III A was 34.80, 10 cases in stage III B was 54.36, 5 cases in stage III C was 51.00, 1 case in stage IV C was 50.80. The highest proliferative index was observed in stage I. [Table 3]

Table 1: Distribution of cases in the study

		No (%)
Site	Ascending colon	8 (19%)
	Caecum	6 (14.3%)
	Descending colon	3 (7.1%)
	Recto-sigmoid junction	3 (7.1%)
	Rectum	10 (23.8%)
	Sigmoid colon	8 (19%)
	Transverse colon	4 (9.5%)
Histological type	Adenocarcinoma	34 (81%)
	Mucinous adenocarcinoma	7 (16.7%)
	Squamous cell carcinoma	1 (2.4%)
Grade	Well, differentiated	14 (41.2%)
	Moderately differentiated	16 (47%)
	Poorly differentiated	4 (11.8%)
Stage	I	3 (7.1%)
	II A	11 (26.2%)
	II B	6 (14.3%)
	II C	5 (11.9%)
	III A	1 (2.4%)
	III B	10 (23.8%)
	III C	5 (11.9%)
	IV C	1 (2.4%)

Table 2: Values of the Ki67 index in the study

Ki67 Index	**No of cases**	**Min-Max**	**Mean STD**
Normal intestinal mucosa	15	2.6-18.2	9.992 ± 4.910
Upper and lower values	42	14.2-74.6	50.498 ± 15.8879

Table 3: Ki67 index in different stages in the study

	Mean STD	**Min-Max**	**95% Confidence Interval for Mean**	
			Lower Bound	**Upper Bound**
Well, differentiated	54.157 ± 11.7995	36.5-66.8	47.344	60.970
Moderately differentiated	50.838 ± 15.5313	24.3-74.6	42.561	59.114
Poorly differentiated	63.950 ± 6.6496	59.1-73.4	53.369	74.531
Mucinous adenocarcinoma	33.343 ± 16.9463	14.5-67.5	17.670	49.016
Squamous cell carcinoma	60.100	60.1-60.1	.	.
STAGE I	61.800 ± 2.2650	59.4-63.9	56.174	67.426
II A	47.100 ± 12.0864	30.3-65.8	38.980	55.220
II B	47.767 ± 16.8435	24.3-66.8	30.091	65.443
II C	49.320 ± 12.0157	35.0-60.1	34.401	64.239
III A	34.800	34.8-34.8	.	.
III B	54.360 ± 16.8324	23.7-71.4	42.319	66.401
III C	51.000 ± 29.0411	14.5-74.6	14.941	87.059
IV C	50.800	50.8-50.8	.	.

Table 4: Cases of stage I and II with grade and Ki67 index

	Grade	**No of cases**	**Ki 67 index of each case**	**Mean ki67 of each grade**
Stage I	Grade 1	1	63.9	63.9
	Grade 2	2	59.4 62.1	60.75
Stage II A	Grade 1	6	38 38.9 40.2 47.8 63.3 64.2	48.683
	Grade 2	4	38.1 45 46.8 65.8	48.925

ISSN (O): 2687-5365; ISSN (P): 2753-6556

	Mucinous	1	30.3	30.3
Stage II B	Grade 1	3	36.5 65.6 66.8	56.30
	Grade 2	3	24.3 41.3 52.1	39.23
Stage II C	Grade 1	1	54.6	54.6
	Grade 3	1	59.1	59.1
	Mucinous	2	35 37.8	36.4
	Squamous cell carcinoma	1	60.1	60.1

Table 5: Cases of stage III and IV with grade and Ki67 index

	Grade	**No of cases**	**Ki 67 index of each case**	**Mean ki67 of each grade**
Stage III A	Grade 1	1	34.8	.
Stage III B	Grade 1	2	63.2 64.7	63.95
	Grade 2	4	25.5 50.8 53.5 71.4	50.30
	Grade 3	2	59.5 63.8	61.65
	Mucinous	2	23.7 67.5	45.60
Stage III C	Grade 2	2	67.9 74.6	71.25
	Grade 3	1	73.4	73.4
	Mucinous	2	14.5 24.6	19.55
Stage IV C	Grade 1	1	50.8	.

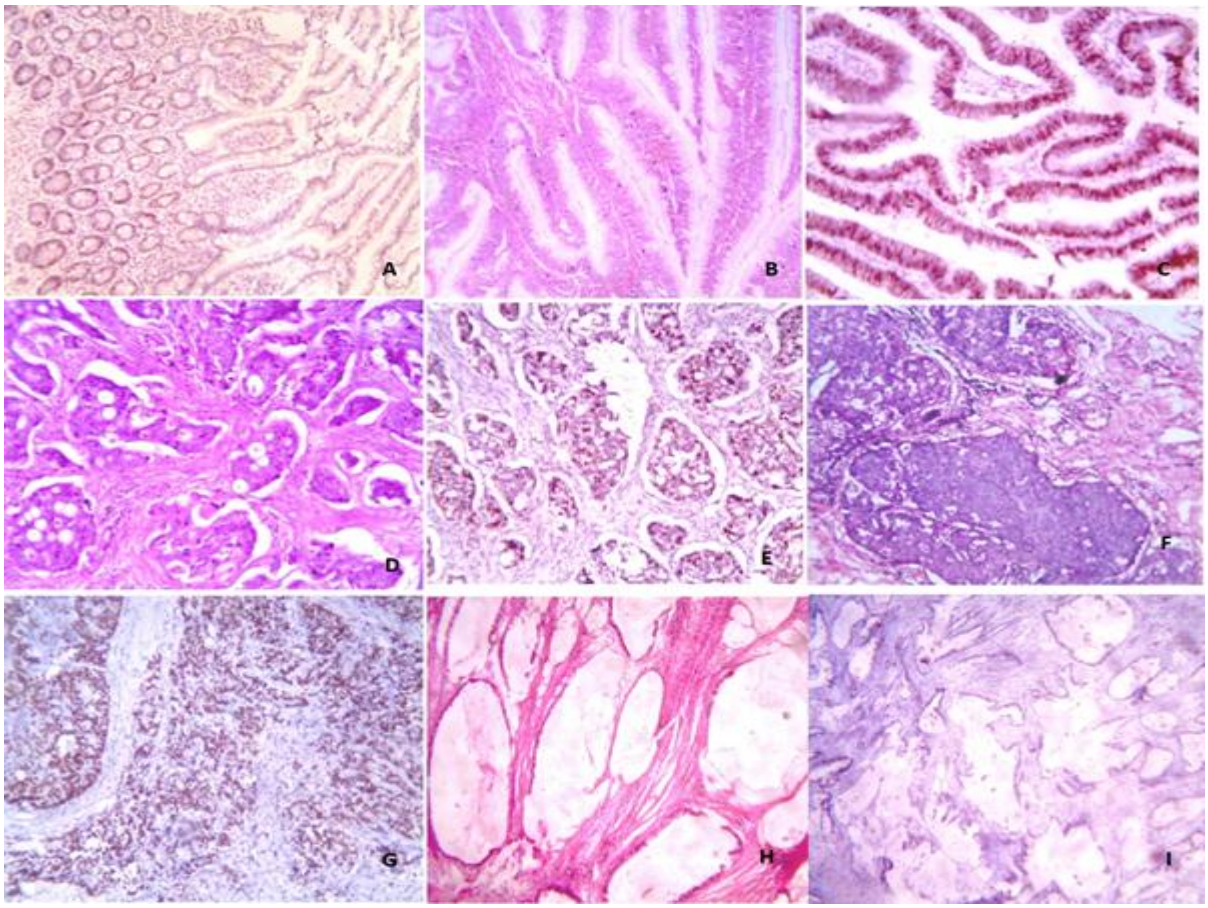

Figure 1: Photomicrograph Showing Ki67 Immunostaining. A: Normal Intestinal Mucosa, B: Well-Differentiated Adenocarcinoma - H&E Stain, C:Well-Differentiated Adenocarcinoma, D:Moderately-Differentiated Adenocarcinoma - H&E Stain, E:Moderately-Differentiated Adenocarcinoma, F:Poorly-Differentiated Adenocarcinoma - H&E Stain, G:Poorly-Differentiated Adenocarcinoma, H:Mucinous Adenocarcinoma - H&E Stain, I:A Mucinous Adenocarcinoma

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Among the 3 cases in stage I, 1 belongs to grade 1, which has a Ki67 index of 63.9 and 2 belongs to grade 2, which has a mean Ki67 index of 60.75. Among the 11 cases in stage II A, 6 belonged to grade 1, with a mean Ki67 index of 48.683. Four cases belonged to grade 2, with a mean Ki67 index of 48.925 and 1 was the mucinous adenocarcinoma with a Ki67 index of 30.3.

Among the 6 cases in stage II B, 3 belong to grade 1, which had a mean Ki67 index of 56.30 and 3 to grade 2, which had a mean Ki67 index of 39.23. Among the 5 cases in stage II C, 1 case belonged to grade 1, which had a Ki67 index of 54.6, 1 case belonged to grade 3, which had a Ki67 index of 59.1 and 2 cases were the mucinous adenocarcinoma which had a mean Ki67 index of 36.4, 1 case was a squamous cell carcinoma which had the Ki67 index of 60.1. [Table 4]

One case in stage III A, grade 1 adenocarcinoma, had a Ki67 index of 34.8. Among the 10 cases in stage III B, 2 belong to grade 1, with a mean Ki67 index of 63.95. Four cases belonged to grade 2, which had a mean Ki67 index of 50.30, 2 cases belonged to grade 3, which had a mean Ki67 index of 61.65 and 2 cases were the mucinous adenocarcinoma which had a mean Ki67 index of 45.60. Among the 5 cases in stage III C, 2 cases belonged to grade 2, which had the mean Ki67 index of 71.25, 1 case belonged to grade 3, which had a Ki67 index of 73.4 and 2 cases were the mucinous adenocarcinoma which had a mean Ki67 index of 19. One stage IV C case, grade 1 adenocarcinoma, had a Ki67 index of 50.8. [Table 5]

DISCUSSION

The prognosis of mucinous adenocarcinoma has been controversial. Tumours with grade 1 and 2 differentiation are associated with a better prognosis. Quantifying cell proliferative activity in neoplasia is currently the subject of considerable investigation.[9-12] In our study of 42 cases, the rectum was the commonest site of occurrence of colorectal carcinoma. Phipps et al,[13] in their study of 3284 cases of colorectal carcinoma, found that 24% of cases were located in the rectum, and the rectum was the commonest site of occurrence of colorectal carcinoma. This observation correlates well with our study.

Out of the 42 cases in our study, most of the colorectal carcinomas were adenocarcinomas. This correlated well with the study conducted by Fleming et al,[14] which stated that more than 90% of colorectal carcinomas were adenocarcinomas. Among the 34 cases, moderately differentiated adenocarcinoma was the most common histopathological grade observed. In addition, Sen et al,[15] also observed moderately differentiated adenocarcinoma as the most common histopathological grade in their study, similar to ours. The maximum number of cases at presentation were in stage II in our study. Li et al,[16] observed a maximum number of cases in stage III at presentation.

In our study, the mean Ki-67 index of 9.99% was observed in cases with normal intestinal mucosa, with values ranging from 2.6% to 18.2 %. Berenzi et al,[17] observed the Ki-67 index in normal intestinal mucosa from 1.5% to 17 %. The ki67 index was calculated for 42 colorectal carcinomas ranging from 14.5% to 74.6%, with a mean Ki67 index of 50.49%. Bhaghyalakshmi et al,[18] assessed the Ki-67 proliferation index in colorectal carcinoma, which ranged from 8.4% to 84.4%. There is a significant difference in the mean Ki-67 index of the normal intestinal mucosa and colorectal carcinoma cases, which is about 5 times the normal intestinal mucosa index.

Regarding the histological grade of colorectal adenocarcinomas, the tumour proliferative activity detected with the Ki-67 antibody increased with the decrease of cell differentiation. Furthermore, the stepwise increase of the mean Ki-67 index with the dedifferentiation of the colorectal adenocarcinomas indicates a cell hyperproliferation in poorly differentiated adenocarcinomas. Sen et al,[15] observed that the mean Ki-67 index of well-differentiated, moderately differentiated and poorly differentiated adenocarcinomas were 14.25, 31.34 and 43.08, which was statistically significant. In a study by Georgescu et al,[19] the mean Ki-67 index increased with the histological grade of adenocarcinomas and had the following values: 20% in well-differentiated adenocarcinoma (ranges 14-23%) and 34% in moderately (ranges 18-57%). In addition, the difference between grade 2 and 3 adenocarcinomas was significant ($p<0.05$). These findings correlated with our present study of 42 cases of colorectal carcinomas, where the difference between grade 2 and grade 3 adenocarcinomas was significant.

Out of 42 cases in the study, 8 cases had a high proliferative index despite having a low grade and stage, 2 cases had a low proliferative index despite being in the higher stage, and 1 case of mucinous adenocarcinoma had a high proliferation index. Georgescu et al,[19] observed a high proliferation index of 55% in cases of mucinous adenocarcinoma. High tumour proliferative index in mucinous adenocarcinoma, if associated with microsatellite stability, had a better response to antineoplastic chemotherapeutic agents and radiation therapy. Kubota et al,[20] in their study, observed stage I tumours had a high proliferation index.

In our study, 3 cases in stage I also had a high proliferation index. Hence the other 5 cases with high proliferation index in the lower stage needs to be followed up carefully for recurrence and distant metastasis. The 2 cases with a low proliferative index in the higher stage could have better survival.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Among the 42 cases, 8 (19%) had a Ki67 proliferation index that didn't correlate with their stage and grade at presentation. These 8 cases (19%) could show a different biological behaviour from the other cases in the same stage and grade regarding their Ki67 proliferation index. Thus, by calculating the Ki67 proliferation index for cases of colorectal carcinoma, in addition to the pathological staging and grading, we were able to add a valuable supplementary prognostic indicator regarding the biological behaviour of the tumour. Hence Ki67 proliferation index, along with the histological grade and stage of the tumour, could be an additional tool in deciding the prognosis and further management of the patient.

CONCLUSION

All 42 cases of colorectal carcinomas showed positive nuclear immunohistochemical staining for the proliferative marker, Ki-67. The Ki-67 index increased with the histological grade of colorectal adenocarcinomas, and the mucinous adenocarcinomas had a low proliferating index. However, not all cases in the study showed a direct correlation between tumour grade, stage and Ki67 index. Forty-two cases with adenocarcinoma had a proliferation index that didn't match their stage and grade at presentation. These cases' prognosis and biological behaviour could vary from the other patients in the same stage and level of tumour development. An immunohistochemical study of the Ki67 proliferation index in cases of colorectal carcinoma was found to provide an additional clue regarding the biological behaviour of many tumours. Furthermore, it could help predict the prognosis of colorectal carcinomas.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556